Complete Summary

GUIDELINE TITLE

Systemic adjuvant therapy for patients at high risk for recurrent melanoma.

BIBLIOGRAPHIC SOURCE(S)

Melanoma Disease Site Group. Systemic adjuvant therapy for patients at high risk for recurrent melanoma [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Nov [online update]. 32 p. (Practice guideline; no. 8-1). [69 references]

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Recurrent melanoma

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Evaluation
Treatment

CLINICAL SPECIALTY

Dermatology
Internal Medicine
Oncology
Radiation Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make recommendations regarding the appropriate management of patients at high risk for recurrent melanoma

TARGET POPULATION

Adult patients with high risk for malignant melanoma recurrence who are rendered disease-free following resection. High risk is defined as primary melanoma with tumour thickness $\geq$4.00 mm or level V invasion, primary melanoma with in-transit metastases, primary melanoma with regional lymph node metastases which are clinically apparent or detected at elective lymph-node dissection, regional lymph node recurrence, or involved nodes were excised but there was no known primary melanoma.

INTERVENTIONS AND PRACTICES CONSIDERED

Adjuvant Therapy for High-Risk Melanoma

1. Interferon alpha (high-dose OR low-dose) (versus observation OR vaccine)
2. Interferon alpha plus interleukin-2 versus observation
3. Interferon gamma (versus observation)
4. Levamisole (versus placebo OR versus observation)
5. Vaccine therapy (versus placebo OR versus observation)
6. Chemotherapy (dacarbazine versus placebo OR versus observation; dacarbazine in combination versus observation; methyl-CCNU versus observation)
7. Dacarbazine plus interferon versus observation

MAJOR OUTCOMES CONSIDERED

The primary outcome of interest is survival. Quality of life was also considered.

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

1998 Guideline

A MEDLINE search was done for the period 1980 to March 1997. The search terms included the MeSH terms melanoma/therapy, melanoma/drug therapy, and clinical trial, and the text words random: and adjuvant. A search was also done for published practice guidelines, meta-analyses and reviews. PREMEDLINE was

searched in April and August 1997 and in February 1998, using the textwords "melanoma" and "adjuvant", for articles that were not yet indexed in MEDLINE. The Cochrane Library was also searched for reports of systematic reviews and clinical trials. Physician Data Query (PDQ) and the proceedings of the 1996, 1997 and 1998 meetings of the American Society of Clinical Oncology (ASCO) were searched for ongoing trials. Articles found by the searches, cited in the relevant papers or known to members of the Melanoma Disease Site Group were retrieved and reviewed. Early in the evidence collection process, a meeting was held with representatives of three pharmaceutical firms (Janssen Pharmaceutica, Hoffmann-La Roche and Schering-Plough) to seek any additional information about the agents under scrutiny. This was the only time that pharmaceutical companies were invited to participate in the development of this practice guideline.

2002 Update

The original literature search has been updated using MEDLINE (through September 2002), CANCERLIT (through August 2002), the Cochrane Library (Issue 3, 2002) and the proceedings of the 1999-2002 meetings of the American Society of Clinical Oncology.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

1. Randomized controlled trials (RCT) of systemic therapies for the adjuvant treatment of patients with melanoma. Prior to the literature search, four types of treatments were identified as relevant to the guideline question: levamisole, interferon, vaccines and chemotherapy.
2. Trials had to include patients at high risk of recurrence but the study population did not need to be restricted to this group of patients. For this report, high risk is defined by American Joint Committee on Cancer stages IIB and III (please see Appendix 1 of the original guideline document for staging information) and includes primary tumours $\geq$ 4.00 mm thick, regional lymph-node metastases which are clinically apparent at presentation or are detected at lymph node dissection, and regional lymph node recurrence.

NUMBER OF SOURCE DOCUMENTS

1998 Guideline

147 source documents were reviewed; data from 24 reports were used in formulating the recommendations.

2002 Update

Nine additional randomized trials were found by update searches.

Note: Evidence from these studies is not included in this guideline report but has been reviewed by the Melanoma Disease Site Group. The new evidence has been incorporated into a revised practice guideline report that was recently reviewed by

practitioners in Ontario. Once completed, the new report will replace the current practice guideline.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Level I Evidence

Meta-analyses

Randomized controlled trials that are big enough to be either:

i. Positive, with small risks of false positive conclusions, or
ii. Negative, with small risks of false negative conclusions

Level II Evidence

Randomized controlled trials that are too small, so that they show either:

i. Positive trends that are not statistically significant, with big risks of false positive conclusions, or
ii. No impressive trends, but large risks of false negative conclusions

Level III Evidence

Formal comparisons with non-randomized contemporaneous controls

Level IV Evidence

Formal comparisons with historic controls

Level V Evidence

Case-series

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

The guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI) using the methodology of the Practice Guidelines Development Cycle (see companion document by Browman et al). Evidence was

selected and reviewed by two members of the Melanoma Disease Site Group and methodologists.

1998 Guideline

Synthesizing the evidence: Published guidelines for performing meta-analysis deal with issues related to the comparability among studies of the questions being addressed, the patient populations, the interventions and the outcomes. All of the trials selected for inclusion in this report addressed a common question, namely: Does the therapy under investigation, when given as adjuvant treatment, improve survival compared with no treatment? Similar patient groups, albeit with varying risks of recurrence by virtue of entry criteria, participated in the randomized trials. Few trials were restricted to patients at high risk of recurrence (i.e., lesion depth $\geq$ 4.00 mm, or completely resected regional nodal metastases). For trials enrolling patients with a range of risks, survival results were not reported separately for the high-risk subgroup. The treatments evaluated fall into four distinct groups of interventions: interferons, levamisole, vaccines and chemotherapy. Dose or schedule varied within each type of treatment. The majority of studies used an observation-only control arm rather than a placebo control. A summary of the studies included in this report is given in Table 1, in the original guideline document.

The authors pooled trial results within two of the four groups of therapies (levamisole and chemotherapy). Results were pooled across studies using Metaanalyst[0.988] software provided by Dr. Joseph Lau (Boston, MA). Pooled results are expressed as the odds ratio for mortality (with 95% confidence interval [CI]) such that an odds ratio less than 1.0 favours the active treatment group. Data were analyzed using the random effects model. All significance tests are two-sided. Ideally, a meta-analysis would be restricted to high-risk patients as defined above. However, most of the studies were not limited to this group of patients. Although attempts were made to derive information for this group from the study reports or to obtain results directly from investigators, limited relevant data were available.

The authors have not pooled results from trials of interferon or vaccines. Within the interferon trials, there were differences in treatment schedules that the authors believe could significantly affect the results of these investigations. The vaccine trials studied a variety of vaccines that differed in the postulated mechanisms by which they exerted their immunomodulatory effects. Therefore, the authors do not believe that it is appropriate to pool results from these trials.

The trials reviewed can be divided into two groups based on sample size and the associated power of the studies to detect significant differences between the active treatment and control arms. In order to detect a 20% relative difference in five-year survival rates between treatment groups with a significance level of 0.05 and a power of 0.9, 130 patients would be required in each treatment arm. Trials large enough to detect at least this magnitude of effect were designated as level I studies. In assessing the contribution of results from individual trials to the practice guideline, the greatest weight was given to level I trials.

2002 Update

No further pooled analyses have been performed.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

1998 Guideline

Several issues were discussed at the first Melanoma Disease Site Group (DSG) meeting, following a presentation of the evidence from clinical trials, and a subsequent telephone conference to discuss a draft evidence-based recommendation report:

1. Although the recommendations are directed at the entire high-risk population, evidence for some therapies is available only for a broader group of patients while for other therapies benefit can be examined within subgroups at high-risk.
2. The recommendations need to address the issue of previously treated patients, although no evidence is available.
3. One further issue that arose during the deliberations was how to weigh the evidence, particularly across the various treatment approaches. Meta-analysis was considered inappropriate for the interferon and vaccine trials because of important differences in treatments among studies. Instead, studies were classified according to levels of evidence (Appendix 2 in the original guideline document) and results from individual studies were examined.
4. Finally, this practice guideline is based on evidence rather than on consideration of cost.

One DSG member felt that the evidence did not support the use of interferon outside of a clinical trial, and that patients with node-negative or node-unknown high-risk melanoma should be excluded from the practice guideline because there was insufficient evidence in this subgroup. These concerns were also noted in the practitioner feedback survey.

Any recommendation to support an intervention based on the results of one randomized clinical trial can easily be criticized. While it is true that erroneous conclusions can be drawn from any study, no matter how well it is conducted, it is necessary to examine the consequences of both recommending and not recommending a course of action should subsequent evidence confirm or refute the observed benefit.

First, assume that subsequent information does not support the contention that interferon is an effective therapy and in the interim a recommendation has been made in support of its use. Based on the available data, what are the adverse consequences? Will people have been harmed as a result of this recommendation? It would appear the answer to this should be no if present standards of care are observed. Will treated patients have an impaired quality of life? Yes, to the extent that they are able to tolerate the interferon. However, these effects are self-

limited. The final drawback is a result of lost opportunities from utilizing limited resources in support of an activity that would have been proven to be without value.

By contrast, assume that there is no recommendation in support of interferon and that subsequent information supports its role in the treatment of this disease. While resources will not have been consumed and many patients who would not have benefited from the therapy will not have had to endure the side effects of treatment, there will have been nine lives lost for every 100 people not treated during a five-year period after the opportunity to treat would have arisen.

We believe the consequences of not recommending the use of interferon in the presence of high-quality information would be to unnecessarily compromise the welfare of these patients should the results of the Eastern Cooperative Oncology Group (ECOG) 1684 study be confirmed.

The DSG reasoned that the randomized controlled trial (RCT) demonstrating a benefit for interferon was designed for patients at high risk for recurrent melanoma which includes a diverse group of patients matching the population described in the guideline question. The DSG did not believe that it was appropriate to deny interferon therapy to subsets of patients within the high-risk group for whom benefits were not detected in the trials. Until further evidence becomes available it is not possible to determine whether this observed lack of benefit is real or is due to low power because of small sample sizes in some subsets. However, the DSG recognizes this may be a consideration in the discussion about risks and benefits that we recommend should occur with any patient being considered for interferon therapy.

2002 Update

The Melanoma DSG met on November 24, 1998 to consider the preliminary findings of the ECOG 1690 interferon trial and their implications. Preliminary results of the ECOG 1690 trial, released in November 1998 on the National Cancer Institute web site, included a failure to confirm a survival benefit for the use of high dose interferon in the care of patients at high risk for recurrence of their cutaneous melanoma following resection of deep primary lesions (>4.0 mm); a recurrence-free survival benefit which had not translated into a survival benefit with more than 90% of the anticipated events (deaths accounted for; and a similar pattern of the survival curves between the treated group and untreated patients.

The DSG decided to reserve judgement about changing the guideline until a peer-reviewed report of the trial was available. They did, however, add a strong qualifying statement to the practice guideline to alert practitioners to the evidence emerging from the ECOG 1690 trial. The revised document was sent to practitioners in Ontario who treat melanoma with a letter informing them about the trial and the DSG´s discussions.

Members of the Melanoma DSG unanimously agreed that patients currently receiving interferon be informed of the preliminary new information as soon as reasonably possible and, in discussion with these patients, a decision reached about the merits of continuing the therapy. New patients who match the target

population for the current guideline should be informed of the preliminary results of the new study and a decision reached about commencing interferon therapy. If the decision is to pursue interferon therapy, all aspects of the original guideline apply.

Since 1998, a full report of the ECOG 1690 trial and other new evidence has emerged from reviewing and updating activities, and is being reviewed and evaluated by the Melanoma DSG.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

External review by Ontario practitioners was obtained through a mailed survey of 27 practitioners in Ontario (7 medical oncologists, 12 radiation oncologists, 3 surgeons, 2 dermatologists, and 3 others) consisting of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations, and whether the recommendations should serve as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The results of the survey were reviewed by the Melanoma Disease Site Group. Twenty (74%) surveys were returned.

Final approval of the original guideline report was obtained from the Practice Guidelines Coordinating Committee.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary. The recommendations that follow are based on the previous version of the guideline.

Note from the National Guideline Clearinghouse (November 2002): The Melanoma Disease Site Group has rewritten their practice guideline on systematic adjuvant therapy for patients at high risk for recurrent melanoma. A draft of the new guideline, which includes evidence from nine additional randomized trials and

revised recommendations, has recently been reviewed by practitioners in Ontario. Once completed, the new report will replace the current practice guideline.

Statement Added September 2000

Results from the full publication of the Eastern Cooperative Oncology Group (ECOG) 1690 trial are inconsistent with the data used to inform the original 1998 guideline recommendations (below). Results from this trial indicate that neither high-dose nor low-dose interferon showed a survival benefit relative to observation. The Melanoma Disease Site Group is reviewing this evidence and considering the implications of the report.

1998 Recommendations

- There is level I evidence from one randomized trial to support the use of high-dose interferon alpha in the care of these patients.
- In this trial, there was a reduction in mortality at five years from 63% in the control group to 54% in the group treated with interferon. Eleven patients would need to be treated for one patient to derive this benefit; a number-needed-to treat similar to that associated with other adjuvant therapies. Treatment with interferon produces grade 3 or greater toxicity in two-thirds of patients.
- The authors recommend that interferon therapy be used in this high-risk group provided that each patient has been made aware of the relative risks and benefits of this therapy and wishes to proceed.

Definitions

Level I Evidence

Meta-analyses

Randomized controlled trials that are big enough to be either:

i. Positive, with small risks of false positive conclusions, or
ii. Negative, with small risks of false negative conclusions

Level II Evidence

Randomized controlled trials that are too small, so that they show either:

i. Positive trends that are not statistically significant, with big risks of false positive conclusions, or
ii. No impressive trends, but large risks of false negative conclusions

Level III Evidence

Formal comparisons with non-randomized contemporaneous controls

Level IV Evidence

Formal comparisons with historic controls

Level V Evidence

Case-series

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

1998 Guideline

Survival data were available from 22 randomized controlled trials (RCTs) (two trials had two relevant active treatment arms): four RCTs examined the role of interferon alpha, one of interferon gamma, four of levamisole, seven of vaccine therapy, eight of chemotherapy, and one of dacarbazine and interferon in combination. Patient populations varied among these trials but all included the population of interest.

2002 Update

Nine additional randomized trials were found by update searches. Evidence from these studies is not included in this guideline report but has been reviewed by the Melanoma Disease Site Group. The new evidence has been incorporated into a revised practice guideline report that was recently reviewed by practitioners in Ontario. Once completed, the new report will replace the current practice guideline. Eleven relevant comparisons were made in the nine randomized trials published since 1998:

- One trial of interferon gamma versus observation
- Two trials comparing vaccine to placebo or observation
- Five trials comparing low-dose interferon alpha to observation
- One trial of low-dose interferon alpha plus interleukin-2 versus observation
- One trial of high-dose interferon alpha versus observation
- One trial of high-dose interferon alpha versus vaccine

New evidence from two trials is directly relevant to the recommendation for interferon made in the 1998 practice guideline. The 1998 recommendation was based on results of the Eastern Cooperative Oncology Group (ECOG) 1684 trial, which detected a significant improvement in overall survival with high-dose interferon alpha after prolonged follow-up. Another large randomized trial of interferon versus observation (ECOG 1690), published after completion of the original practice guideline, failed to find any survival benefit for high-dose interferon. The second new trial (ECOG 1694) detected a significant survival difference, favouring interferon, between high-dose interferon and a melanoma vaccine.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

1998 Guideline

There are three published trials of adjuvant interferon therapy that measured survival rates; two have been reported in full and one in abstract form. These trials used substantially different doses and routes of administration in different risk groups of patients, and the results cannot be readily combined. One randomized controlled trial (RCT) with high-dose interferon alpha-2b detected a significant improvement in patient survival after prolonged follow-up. In this trial there was a reduction in mortality at five years from 63% in the control group to 54% in the group treated with interferon. Eleven patients would need to be treated for one patient to derive this benefit; a number needed to treat similar to that associated with other adjuvant therapies. A trial of high-dose interferon alpha-2a over a shorter treatment time failed to detect any benefit. A trial of low-dose interferon alpha-2a in a lower risk group of patients has, with short follow-up, shown borderline survival benefit that appears to lessen with time.

Though there is a Canadian RCT demonstrating marginal benefit of adjuvant levamisole for all risk groups of patients, a meta analysis of data from the four levamisole trials did not show a significant survival benefit for levamisole over control.

Data from RCTs do not suggest an improvement in survival with vaccines or chemotherapy.

2002 Update

New evidence from two trials is directly relevant to the recommendation for interferon made in the 1998 practice guideline. The 1998 recommendation was based on results of the Eastern Cooperative Oncology Group (ECOG) 1684 trial, which detected a significant improvement in overall survival with high-dose interferon alpha. Another large randomized trial of interferon versus observation (ECOG 1690), published after completion of the original practice guideline, failed to find any survival benefit for high-dose interferon. A second new trial (ECOG 1694) detected a significant survival difference, favouring interferon, between high-dose interferon and a melanoma vaccine.

POTENTIAL HARMS

- Sixty-seven percent of patients participating in the interferon alpha-2b study experienced severe (grade 3 or greater) toxicity with 9% of patients having life-threatening toxicity. Thirty-seven percent of patients had dose reductions or delays in treatment because of toxicity. Two deaths due to interferon, linked to inadequate monitoring of liver function tests in those patients, occurred early in the study. No further treatment-related mortality at this dose has been described in this or a subsequent study.
- Morbidity from levamisole is generally mild and reversible but did result in the discontinuation of therapy in 41% of patients in the National Cancer Institute

of Canada (NCIC) study. Most patients who discontinued levamisole because of toxicity did so because of gastrointestinal intolerance or musculoskeletal symptoms. No treatment related mortality was observed in the randomized trials of levamisole.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Melanoma Disease Site Group. Systemic adjuvant therapy for patients at high risk for recurrent melanoma [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Nov [online update]. 32 p. (Practice guideline; no. 8-1). [69 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1998 May 27 (updated 2002 Nov)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long Term-Care

GUIDELINE COMMITTEE

Provincial Melanoma Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of members past and present, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Melanoma Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

Please note: This guideline has been updated. The National Guideline Clearinghouse (NGC) is working to update this summary.

GUIDELINE AVAILABILITY

Electronic copies of the updated guideline: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Systemic adjuvant therapy for patients at high risk for recurrent melanoma. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2002 Nov. Various p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 1999. The summary was updated by ECRI on August 10, 2001 and verified by the guideline developer as of

August 22, 2001. This NGC summary was updated by ECRI on March 20, 2003. The information was verified by the guideline developer on May 8, 2003.

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